Notice of Allowability	Application No.	Applicant(s)	
	10/815,262	ENGELHARDT ET AL.	
	Examiner	Art Unit	
	KEVIN K. HILL	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *December 10, 2009*.

2. ☒ The allowed claim(s) is/are *1,2,9-24,43,44,46,48-50,62,66 and 67*.

3. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date December 10, 2009, January 14, 2010
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☒ Interview Summary (PTO-413), Paper No./Mail Date *January 6, 2010* .
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

Detailed Action

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 10, 2009 has been entered.

Amendments

Applicant's response and amendments, filed December 10, 2009, to the prior Office Action is acknowledged. Applicant has cancelled Claims 3-8, 25-26, 28, 33-42, 45-47, 52, 54, 60-61 and 63-65, withdrawn Claims 27, 29-32, 51, 53 and 55-59, amended Claims 1, 21, 23-24, 43 and 62, and added new claims, Claims 66-67.

NOTICE OF ALLOWANCE

1. **Claims 1-2, 9-24, 43-44, 46, 48-50, 62 and 66-67 are allowable.**

The previous rejections in the Office action mailed on August 6, 2009 are withdrawn in view of the amendments. All of the amendments have been thoroughly reviewed and entered.

The Examiner acknowledges and has considered the Engelhardt and Yan Declaration filed under 37 CFR §1.132 on December 10, 2009.

Claims 27, 29-32, 51, 53 and 55-59, previously withdrawn from consideration as a result of a restriction requirement, require all the limitations of an allowable claim. Pursuant to the procedures set forth in MPEP §821.04(a), the restriction requirement among inventions species, as set forth in the Office action mailed on September 18, 2006, is hereby withdrawn and claims 27, 29-32, 51, 53 and 55-59 are hereby rejoined and fully examined for patentability under 37 CFR 1.104. In view of the withdrawal of the restriction requirement, applicant(s) are advised that if any claim presented in a continuation or divisional application is anticipated by, or includes all the limitations of, a claim that is allowable in the present application, such claim may be subject

to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application.

Once the restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. See *In re Ziegler*, 443 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP §804.01.

Information Disclosure Statement

Applicant has filed an Information Disclosure Statements on December 10, 2009 and January 14, 2010, that have been considered. The signed and initialed PTO Forms 1449 are mailed with this action.

Examiner's Amendment

2. **An Examiner's amendment to the record appears below.** Should the changes and/or additions be unacceptable to Applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this Examiner's amendment was given in a telephone interview with Applicant's representative Jan Embretson at 612-373-6959 on January 6 and 13, 2010.

Claim 1 has been re-written as follows:

A method to enhance recombinant adeno-associated (rAAV) transduction of a mammalian cell, the method comprising contacting the mammalian cell at the time of rAAV infection with an amount of an anthracycline and an amount of a tripeptide aldehyde that inhibits proteosome proteolytic activity that together more than additively enhance rAAV transduction.

Claim 27 has been re-written as follows:

The method of claim wherein the anthracycline or tripeptide aldehyde modulates rAAV trafficking in the cell.

Claim 29 has been re-written as follows:

The method of claim 1 wherein the anthracycline or tripeptide aldehyde modulates rAAV nucleic acid degradation in the cell.

Claim 30 has been re-written as follows:

The method of claim 1 wherein the anthracycline or tripeptide aldehyde modulates rAAV protein degradation in the cell.

Claim 31 has been re-written as follows:

The method of claim 1 wherein the anthracycline or tripeptide aldehyde modulates rAAV transport to the nucleus.

Claim 32 has been re-written as follows:

The method of claim 1 wherein the anthracycline or tripeptide aldehyde modulates viral genome transport to the nucleus.

Claim 43 has been re-written as follows:

A method to enhance rAAV transduction of a mammalian cell, the method comprising contacting the mammalian cell at the time of rAAV infection with an amount of a peptide that inhibits proteosome proteolytic activity and an amount of an anthracycline, selected from the group consisting of doxorubicin, duanorubicin, idarubicin and epirubicin, that together more than additively enhance rAAV transduction.

Claim 51 has been re-written as follows:

The method of claim 43 wherein the anthracycline or peptide modulates microfilaments or microtubules.

Claim 53 has been re-written as follows:

The method of claim 43 wherein the anthracycline or peptide modulates rAAV trafficking in the cell.

Claim 55 has been re-written as follows:

The method of claim 43 wherein the anthracycline or peptide modulates rAAV nucleic acid degradation in the cell.

Claim 56 has been re-written as follows:

The method of claim 43 wherein the anthracycline or peptide modulates rAAV protein degradation in the cell.

Claim 57 has been re-written as follows:

The method of claim 43 wherein the anthracycline or peptide modulates rAAV transport to the nucleus.

Claim 58 has been re-written as follows:

The method of claim 43 wherein the anthracycline or peptide modulates viral genome transport to the nucleus.

Claim 59 has been re-written as follows:

The method of claim 43 wherein the anthracycline or peptide modulates subcellular localization of proteosomes.

3. **The following is an Examiner's statement of reasons for allowance:** The prior art recognized the existence of peptide compounds that inhibit proteasome protease activity and those of ordinary skill in the prior art had practiced contacting mammalian cells, *in vitro* and *in vivo*, with said peptide compounds. Similarly, the prior art recognized the existence of anthracycline compounds and those of ordinary skill in the prior art had practiced contacting mammalian cells, *in vitro* and *in vivo*, with said anthracycline compounds. The prior art recognized that peptide protease inhibitors enhanced rAAV transduction of mammalian cells, and that at least one proteasome protease inhibitor can modulate: i) rAAV trafficking in the cell, ii) rAAV nucleic acid degradation in the cell as measured by accumulation of intracellular rAAV

genomes, iii) rAAV protein degradation, iv) rAAV transport to the nucleus, v) viral genome transport to the nucleus, vi) microfilaments or microtubules, and vii) subcellular localization of proteosomes. However, the prior art does not teach or fairly suggest that rAAV transduction of a mammalian cell would be enhanced to an at least greater than additive amount when the combination of an effective amount of an anthracycline and a peptide proteasome protease inhibitor are present in the cell at the time of rAAV infection, as compared to either the anthracycline or the peptide proteasome protease inhibitor alone.

Any comments considered necessary by Applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Conclusion

4. **Claims 1-2, 9-24, 27, 29-32, 43-44, 46, 48-51, 53, 55-59, 62 and 66-67 are allowed**.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Kevin K. Hill whose telephone number is 571-272-8036. The Examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kevin K. Hill/
Examiner, Art Unit 1633